Spread and mitigation of antimicrobial resistance at the wildlife-urban and wildlife-livestock interfaces

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ABSTRACT
Antimicrobial resistance (AMR) is a health issue common to all One Health domains. Scientific understanding of what drives AMR and how it spreads is continually expanding. One such dimension of this expanding base of knowledge is the role wildlife populations play as reservoirs and spreaders of AMR. Indirect and direct sharing of resistant pathogens between wildlife and domestic animals occurs in a variety of ways across both the natural and built environment. Though AMR is found across much of the Earth’s biome naturally, elevated levels in wildlife are largely attributed to the use of antimicrobials in human and veterinary medicine, along with other uses of antimicrobials in human industry. On the basis of current research, wildlife species appear to be net recipients of AMR overall. However, wildlife can carry and spread AMR across individual ecosystems and to other ecosystems via water, soil, arthropod vectors, and several other routes of conveyance. In addition to creating potential health issues for wildlife animals themselves, this potentially poses risks for both companion and production animals. This is especially due to urban/suburban and rural wildlife, respectively. If health practitioners and other stakeholders are adequately aware, measures can be taken to reduce risks across each interface discussed. The companion Currents in One Health article by Vezeau and Kahn, AVJVR, June 2024, addresses in further detail the many wildlife reservoirs of AMR that are currently identified, as well as directions for further research.

Keywords: wildlife, public health, biosecurity, epidemiology, antimicrobial resistance

Introduction
Antimicrobial resistance (AMR) is recognized as a serious threat to health globally.¹ Veterinary practitioners play a critical role in identifying and mitigating AMR in collaboration with other professional sectors using a One Health approach. Significant attention has been given to antimicrobial use (AMU) and AMR in livestock populations, with some more recent efforts focusing on companion animal health. There is currently an incomplete understanding of how AMR, in the form of resistant bacteria (ARB), plasmid DNA and individual genes (ARGs), and antimicrobial residues, spreads from different sources.² In AMR research, the environmental domain of One Health is the most understudied due in part to difficulty with pathogen surveillance across such a wide-spanning sector. Because of this, nondomestic animals remain a relatively ill-understood component of AMR spread. Nonetheless, they serve as a key link between the environmental and animal domains of One Health via direct and indirect contact, fecal contamination, and other shared environmental resources.³

Antimicrobials are produced naturally by many organisms across much of Earth’s biome, and thus AMR can be found in a vast array of ecosystems, even in the absence of human activity.⁴ The spread of AMR is also aided by horizontal transmission, wherein ARGs are carried on mobile genetic elements such as plasmids or transposons that can be transferred between microorganisms. This is particularly common in bacteria and can even be mediated by viruses.⁵,⁶ However, AMU in human activities such as medicine and agriculture appears to substantially increase AMR concentrations within the context of these activities, such as inside hospitals and livestock operations, as well as in surrounding environments.⁷ The exact impact that such anthropogenic activity can have on AMR across One Health sectors is a matter of debate. However, there is relative agreement that spread can occur between humans, animals, and the environment.

Current Status of AMR in Domestic and Farmed Animals
Antimicrobial resistance is everywhere and long predates the use of antimicrobials in medicine. The
presence of pathogen resistance combinations of highest concern to animal health should be the focus of AMR surveillance and mitigation efforts. Abnormally high resistance, or antimicrobial residues, connected by spatiotemporal proximity or other routes of transmission should be taken as the strongest evidence of anthropogenic drivers of AMR.

Antimicrobial resistance in important bug-drug combinations has been on the rise globally across terrestrial food animal species, especially in the hinterland areas of large human population centers. Globally, AMR in livestock is generally highest for the antimicrobials most often used in them, such as tetracyclines, sulfonamides, and penicillins. In the US, common forms of AMR include ciprofloxacin-resistant Salmonella spp, ciprofloxacin resistance in Campylobacter jejuni, and multidrug-resistant Salmonella in poultry isolates. Extremely drug-resistant Salmonella, resistant to multiple indicated lines of antibiotic treatment, is also present in cattle, swine, and chickens.

Aquaculture is another expanding industry with an increasingly understood AMR profile. Though holistic analyses on a country-by-country basis are uncommon, data from aquaculture operations in Asia suggest that AMR has been relatively constant over the past several decades, with significant resistance profiles for aquatic food seen for penicillins, sulfonamides, tetracyclines, and macrolides.

In at least the US, large-scale data collection on AMR has historically been less robust and less centralized than for livestock. Antimicrobial resistance is often reported at a more local level or through a diagnostic laboratory network in the US, but there has been a push to surveil AMR in companion animals holistically alongside that in livestock and humans.

**Likely Drivers and Routes of Spread**

Across all One Health domains, AMU is generally discussed as the predominant driver of increases in AMR. This includes use in human populations, animal populations, and even plant populations. Antimicrobial use in humans is likely the most prominent driver of the most clinically important bug-drug combinations in human medicine. In at least production animal settings, veterinary AMU similarly seems to be the strongest correlate of AMR in animals. Given that antimicrobials are not used at scale in wildlife, one might conclude they are net recipients of AMR, though evidence is still emerging and must be considered on a case-by-case basis. Thus, our understanding is incomplete regarding what drives AMR in wildlife populations, what the magnitude of any given driver is, and what implications this has for veterinary and public health. Figure 1 demonstrates the species understood to be relevant to the spread of AMR.

**Anthropogenic activity**

Antimicrobial use has a significant impact on AMR in wildlife, with the potential for wildlife to serve as a reservoir and “mixing vat” of ARB and ARGs. This is particularly concerning given the potential for wildlife to spread ARB to humans and other animals. The use of antimicrobials in animals and humans can contribute to the development of resistance in both animal and human pathogens. However, the role of wildlife in the spread of AMR is complex, with some work suggesting that resistance in commensal bacteria of wildlife is not only by AMU. Nevertheless, much of the presence of ARGs and ARB in wild animals appears to be associated with AMU in human activity. Antimicrobial resistance in wildlife is also exacerbated by these anthropogenic inputs and the foraging behavior of wild animals.

Additionally, wild animals in captivity, such as in zoos, have the potential to act as reservoirs and spreaders of ARB. The presence of AMR in these animals has been confirmed, albeit with high variability of resistant isolates found between species. The spread of AMR in this wildlife appears to be similarly linked to human activities and the contamination of natural habitats.

Research on the presence of AMR in wildlife with minimal human influence—those thought to have microbiomes and pathogens most representative of a time predating the discovery of antibiotics—has yielded mixed results. Some studies have found significant levels of AMR in wildlife, including wild birds and mammals. However, the prevalence of ARB in certain wild animals in Germany was found to be low, possibly due to low exposure to antimicrobials and ARB. Additionally, Norwegian Polar bears, relatively isolated from human activity, were found to have low levels of ampicillin resistance in their gut flora. This also suggests ingestion of AMR and further spread throughout and from the gut may be a prominent route of dissemination.

**Urban wildlife–companion animal interface**

Urban wildlife populations and pets can serve as reservoirs and vectors for the spread of AMR. Companion animals such as dogs and cats can contribute to the spread of AMR due to their close contact with humans. Wild animals, especially those living in human-influenced environments, can easily acquire and spread AMR. Wild birds play a significant role in the transmission of ARGs to and from human population centers. Pets, such as dogs and cats, can also act as reservoirs of AMR, with transmission occurring between pets, owners, and veterinary staff. Insects such as houseflies and cockroaches can serve as a link between even rural areas and the urban environment for the transmission of AMR traits.

**Livestock–wild vertebrate interface**

Wildlife can act as a reservoir and spreader of AMR, with those that eat meat and spend time in proximity to humans being particularly at risk. Other work has demonstrated that the development of AMR in game species is influenced by factors including farming practices and human contact. The occurrence of ARB in wildlife is associated with anthropogenic inputs into the environment and wildlife taxonomy, among
many other factors. However, the role of wildlife in the spread of AMR may not solely be driven by anthropogenic factors, as resistance can also be found in wildlife living in areas without human interaction. The transmission of ARB from human contact surfaces to wild birds has been documented, highlighting the possibility this may occur for livestock as well. Wild birds are further emphasized as potential spreaders of ARB given the migratory nature of some species. Manure and shared water and food resources are hypothesized to be among the most significant routes of AMR spread between wildlife and livestock. This may be especially true when manure is used to grow crops or other plants or wildlife animals defecate in these areas, representing a multidirectional route of AMR transfer. The presence of ARGs in scavengers such as vultures further underscores the potential for transmission and benefits of preventive biosecurity on livestock operations. Researchers further emphasize the role of wild birds in the global transmission of AMR in these settings.

Waste and water effluents
Significant contributors to the environmental spread of antimicrobials, ARGs, and ARB include human waste treatment effluents, runoff from cropland amended with livestock waste, and direct livestock waste effluents. Antimicrobial resistance gene concentrations in swine and chicken waste, likely representative of resistances most relevant to production animal medicine, is 1,000 to 100,000 times higher than that found even from human-source effluents. Though not universally practiced, wastewater treatment can be used to significantly reduce a
variety of ARGs and ARB, with a smaller effect on antimicrobial concentration.\textsuperscript{35,36}

Wastewater effluents play a significant role in the spread of AMR to other wildlife populations as well. Wastewater has a strong impact on the transmission of ARGs and ARB in the environment.\textsuperscript{20,37} It serves as an overall significant reservoir for AMR.\textsuperscript{38} Antibiotic resistance genes can spread diffusely in the aquatic environment, including river systems.\textsuperscript{39-41} This can then be transmitted to much of the rest of the biosphere.\textsuperscript{20} The role of wildlife in the dissemination of AMR is complex, with factors such as human influence, animal farming practices, and ecological and biological traits of the host playing a significant role.\textsuperscript{17,31,42} Wildlife AMR is not only increased by human activity, and the geospatial patterns and prevalence of resistance are highly variable across wildlife.\textsuperscript{14} Wildlife species can in turn act as reservoirs and pathways for the spread of AMR, highlighting the need for further research in this area.\textsuperscript{26,43}

Fish are among the most common clade of wildlife species inhabiting surface water ecosystems receiving wastewater effluents. River systems downstream from water treatment facilities have been shown to carry antimicrobials common in human use. These antimicrobials are also found in the fish in these environments. However, the fish ARB did not have resistances proportional to the antimicrobial levels in the aquatic environment.\textsuperscript{44} Anthropogenic antimicrobial and ARB runoff also leads to increased AMR in groundwater and the ocean.\textsuperscript{7}

In addition to wastewater, certain forms of industrial runoff can spread AMR to wildlife populations through the release of ARGs and ARB into the environment.\textsuperscript{20,37} This is also the case in operations utilizing or manufacturing antimicrobials. This can occur through the discharge of wastewater from treatment plants, which can modify the characteristics of receiving streams and favor the spread of resistance in microbial communities.\textsuperscript{37} The presence of ARGs in river biofilms, even far downstream of the discharge points, further highlights the potential for the spread of resistance.\textsuperscript{37} General urban runoff waters can also contribute to the dissemination of antibiotic resistance.\textsuperscript{45} The use of untreated wastewater for urban agriculture, a common practice in low- and middle-income countries, can further exacerbate the spread of resistance.\textsuperscript{46} These findings underscore the need for effective wastewater treatment and management strategies to mitigate the spread of AMR to wildlife populations.

**Arthropod vectors**

Arthropods, including insects and ticks, play a significant role in the spread of AMR in wildlife. Their ability to spread pathogens such as ARB may be particularly salient for nonmigrating vertebrates.\textsuperscript{17,20} Other work has highlighted the role arthropods play in the development and propagation of antifungal resistance.\textsuperscript{47}

Insects act as carriers and potential spreaders of ARB. Some insect species serve to connect many nodes in AMR as well as human and veterinary health via contact with feces and waste, surface water, rodents, birds, pets, and livestock.\textsuperscript{20,48} Insects can act as reservoirs and vectors for AMR and transmit through direct contact, food contamination, and horizontal transfer of ARGs.\textsuperscript{49} Insects associated with food animals, such as houseflies and cockroaches, are a direct link between animal farms and urban communities for AMR.\textsuperscript{30} Additionally, “filth flies” can also play a significant role in the spread of AMR between wildlife animals and other hosts, including humans and domestic animals.\textsuperscript{49,50}

Ticks spread AMR in wildlife through a combination of factors. First, their role as vectors for a wide range of pathogens, including those with AMR, contributes to the spread of resistance.\textsuperscript{51} Tick-borne infections are often associated with wildlife animal reservoirs, and coinfection with multiple pathogens is common, creating a “melting pot” effect.\textsuperscript{52} The emergence of tick-borne diseases in domestic animals, and their increasing range as vectors, further contributes to the increasing circulation of tick-borne bacterial pathogens.\textsuperscript{53} The use of anti-tick and transmission-blocking vaccines has been proposed as a potential strategy to disrupt the spread of tick-vec
tored disease.\textsuperscript{54} However, the development of these vaccines is hindered by gaps in our understanding of tick biology and the tick-pathogen-host interface.\textsuperscript{55}

Thus far, the role of arthropods and arthropod-wildlife interactions in AMR spread is dynamic and vastly multifactorial, inclusive of anthropogenic and environmental drivers.\textsuperscript{14,46} Therefore, further work is needed to have a more robust understanding of transmission dynamics between insects, wildlife, and other sectors.

**Wildlife AMR Risk Assessment and Reduction**

Wildlife animals play a significant role in the spread of AMR, with omnivores, carnivores, and those most closely associated with human society being seen as carriers with the highest risk.\textsuperscript{17} They act as reservoirs and vectors for the global dissemination of ARGs, including those to the highest-priority antimicrobials.\textsuperscript{22,25} The presence of ARGs in wildlife is a sign of anthropic pollution, and once present, wildlife can contribute to their transmission across different ecosystems.\textsuperscript{20} This is particularly concerning given the potential impact of wildlife AMR on human health and the environment.\textsuperscript{16} The prevalence of ARB in wild birds and mammals further underscores their role as important host reservoirs and potential vectors for the spread of ARB.\textsuperscript{15} Wildlife can also contribute to the transmission of bacterial pathogens and AMR to the food chain.\textsuperscript{56}

**Risk to humans**

Though our overall focus is veterinary health, the risk that wildlife poses to humans is better characterized for humans than for domestic animals. Novel risk analysis frameworks have been developed for such purposes in China.\textsuperscript{57} This work additionally evidences human activity increasing AMR
in wildlife and highlights the potential for common human pathogens, including *Mycobacterium tuberculosis*, *Bordetella pertussis*, *Staphylococcus* spp, *Streptococcus* spp, *Yersinia* spp, and *Vibrio cholera*. Raccoons are more liable to be net recipients of AMR than drivers when compared to human populations. Thus, humans appear to pose more of an AMR threat to these wildlife populations than vice versa. However, work on wildlife zoonoses in Spain demonstrates that wildlife-to-human AMR risks are non-negligible and likely higher for wildlife that readily traverses into and throughout the built environment. This research also highlighted feces as a route of spread, suggesting that enteric pathogens are a particular concern.

**Companion animals**

Wild birds and mammals have been identified as important reservoirs and potential vectors for the spread of ARB. Pets, in turn, can act as reservoirs of ARB, with the potential for transmission to humans. The judicious use of antimicrobial agents in pets is crucial to mitigate this risk. Wildlife animals can pose a significant risk to pets in terms of AMR. They can act as reservoirs and vectors for ARB, potentially leading to the spread of ARGs across different ecosystems. Insects, rodents, and pets, including dogs and cats, can also harbor and spread AMR, further complicating the issue. This highlights the need for continued surveillance and monitoring of AMR in wildlife and pets to better understand and mitigate these risks.

**Livestock**

Antimicrobial resistance in wildlife poses a significant risk to livestock, with potential implications for public health. Studies have found that wild birds and mammals can harbor ARB, including multidrug-resistant phenotypes, which can be transmitted to livestock. The presence of AMR in wildlife is not solely driven by human activities, suggesting a complex interplay of factors. The spread of AMR in wildlife is influenced by human activities, with certain species at higher risk of carrying and spreading ARB. Therefore, a comprehensive approach is needed to address the risks of AMR in wildlife to livestock, including surveillance, reduction of AMU, and understanding the complex ecological factors involved.

**Food chain**

Antimicrobial resistance in wildlife poses a significant risk to the food chain, with potential implications for public health. Studies have identified a range of ARB in wild birds and mammals, including *Escherichia coli*, *Salmonella*, and *Campylobacter*. The spread of these bacteria can occur through various routes, including direct contact with contaminated food and water sources. The presence of AMR in wildlife is a cause for concern, as it can both evidence and lead to the development of resistant strains in foodborne pathogens. The spread of these bacteria to the food chain can occur through various routes, including direct contamination of food products and cross-contamination during processing. This highlights the need for further research and surveillance to better understand and mitigate the risks associated with AMR in wildlife.

**Threats to wildlife conservation**

Though the relevance of AMR in wildlife is often framed in its importance to veterinary and public health, it can also be of consequence to the wildlife populations themselves. Certain species are at higher risk of carrying and spreading ARB. Omnivorous, anthropophilic, and carnivorous species appear to bear a particularly high burden of AMR, with human AMU as a key driver. The presence of AMR in species such as wild boars, roe deer, and wild ducks underscores the need for continuous monitoring and assessment of the role of wildlife as potential victims of resistant infections in addition to reservoirs of ARB. However, it is difficult to discern the role of anthropogenic effects on AMR in wildlife and how current ARB profiles differ from the pre-antibiotic era in their populations. The implications of wildlife AMR on the effects of human and domestic animal health may also help to increase attention on the implications for conservation efforts.

**Conclusion**

Antimicrobial resistance is an increasing driver of morbidity and mortality in veterinary medicine. Though AMR exists naturally, higher resistance for the bug-drug combinations most relevant to animal and human medicine is largely driven by anthropogenic activities. Antimicrobial resistance can then proceed to propagate throughout the environment and be carried by many animals, including wildlife. With our expanding knowledge of AMR in these arenas, mitigating the prevalence of AMR will require further expansion of stewardship and surveillance efforts across all One Health domains. Future work should discern the degree to which different drivers affect the presence of AMR in wildlife and other domains, what antimicrobials influence AMR elsewhere, and what risks this may create for veterinary and human medicine. Clinicians should focus on judicious AMU and take adequate infection prevention measures to decrease the risk of ARB infections from all sources. Making sure antimicrobials stay effective is everyone’s responsibility.

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